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Efficient and convenient preparation of γ-nonalactone, with use of a Dean–Stark trap to remove methanol

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Abstract We describe the development of an efficient and convenient process for preparation of γ-nonalactone. The synthesis was accomplished by free-radical addition of methyl acrylate and *n*-hexanol. A Dean–Stark trap filled with water and *n*-hexanol was used to remove the methanol generated during the process. Orthogonal experiments were performed to optimize the reaction conditions, and the desired product, γ-nonalactone, was produced in better than 70 % yield.

Keywords Preparation · γ-Nonalactone · Dean–Stark trap used to remove methanol · Orthogonal experiments

Introduction

Lactones, also known as furanones, are common in the plant world. They are responsible for the odor of some flowers, fruits, and vegetables. γ-Lactones mainly occur in such fruits as coconut, peach, mango, apricot, passion fruit, and strawberry, among others [1]. γ-Nonalactone, also known as coconut aldehyde, is a valuable lactone for perfumes. Production of γ-lactones catalyzed by lipase [2, 3], by microbial action [4], or via biosynthetic routes [5] has been extensively studied. Lactones can also be prepared by chemical methods [6–11]. The general process for obtaining γ-lactones is cyclization of 3-alkenoic acids by use of 78–80 % sulfuric

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acid [12]. Currently, γ-nonalactone is mainly produced by free-radical addition of acrylic acid (or methyl acrylate) and *n*-hexanol, which are inexpensive and accessible starting materials [13–18]. However, this method requires high pressure [15, 16, 18]; otherwise, the yield would be low [17] because removal of the water (or methanol) generated during the process is an arduous task. We have previously conducted a preliminary study on the preparation of γ-nonalactone by free-radical addition of acrylic acid and *n*-hexanol using a Dean–Stark trap with added anhydrous Na_2SO_4 as desiccant. The anhydrous Na_2SO_4 absorbs the water generated when acrylic acid is heated under reflux in the reaction flask with *n*-hexanol [19, 20]. This process is, however, unsuitable for industrial manufacture.

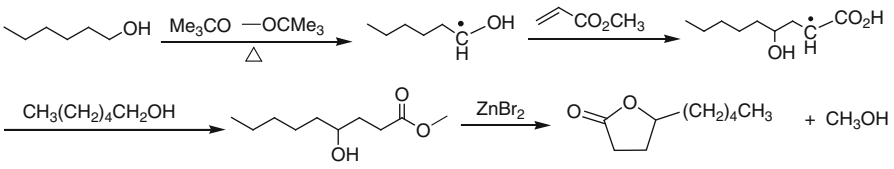
In this study, a Dean–Stark trap containing water was used because of the difficulty of separating the low-boiling-point substances methyl acrylate (bp 80 °C) from the methanol generated (bp 65 °C) at high temperature (~180 °C). The water absorbed the methanol, and the methyl acrylate was returned to the reaction flask with *n*-hexanol. This article describes an efficient and convenient method of preparing γ-nonalactone in better than 70 % yield by free-radical addition of methyl acrylate and *n*-hexanol. To the best of our knowledge, this study is the first to have used a Dean–Stark trap filled with water and alcohol in the free-radical addition of methyl acrylate and alcohol as starting materials to yield γ-lactones.

Results and discussion

The mechanism proposed herein for the preparation of γ-nonalactone by the free-radical addition reaction is shown in Scheme 1 [21].

A Dean–Stark trap filled with water and *n*-hexanol was attached to a flask and used to remove the methanol generated in the process. During the reaction, a mixture of *n*-hexanol, methanol, and other low-boiling-point substances collected in the Dean–Stark trap. Methanol dissolved in water, whereas the raw material methyl acrylate and di-*t*-butyl peroxide (DTBP) were returned to the flask with *n*-hexanol. As a result, methanol was efficiently removed from the system and the reaction proceeded smoothly.

First, the effects of different Dean–Stark trap conditions were investigated. As shown in Table 1, under the control condition in which no Dean–Stark trap was fitted in the flask, the generated methanol could not be removed from the system and led to a low yield of γ-nonalactone (Table 1, entry 1). When the Dean–Stark trap was filled with water, the yield of γ-nonalactone was also low because part of the mixture of water and methanol was returned to the flask, which negatively affected



Scheme 1 Possible mechanism of preparation of γ-nonalactone by the free-radical addition reaction

the reaction (Table 1, entry 2). However, when the Dean–Stark trap was filled with water and *n*-hexanol in the bottom layer and top layer, respectively, γ-nonalactone was produced in higher yield for the reasons described above (Table 1, entry 3).

Our previous research on the preparation of γ-nonalactone by free-radical addition of acrylic acid and *n*-hexanol showed that the optimum reaction temperature and molar ratio of *n*-hexanol to acrylic acid were 180 °C and 7, respectively [19, 20]. Considering that the possible mechanisms in the preparation of γ-lactones by free-radical addition of acrylic acid or by free-radical addition of methyl acrylate to fatty alcohol are similar, we set the molar ratio of *n*-hexanol to methyl acrylate and the reaction temperature to 7 and 180 °C, respectively, in this study.

Orthogonal experiments were performed to optimize the reaction conditions. Four important conditions, feeding time (A), reaction time (B), molar ratio of DTBP to methyl acrylate (C), and molar ratio of $ZnBr_2$ to methyl acrylate (D), were optimized by use of the orthogonal test schedule in Table 2. Each factor had three levels.

The effects of the four factors in Table 2 were investigated by use of orthogonal tests and variance analysis. An orthogonal table $L_9(3^4)$ was used to array the factors, and the results are listed in Table 3. The yield was used to evaluate the efficiency of the synthetic process under different conditions (different factors and levels).

According to Table 3, the effects of the four factors on the yield of γ-nonalactone were in the order: A > B > C > D. The results also showed that the differences between the effect of feeding time and that of reaction time on yield were not obvious. The molar ratio of DTBP to methyl acrylate (C) affected the yield of γ-nonalactone more clearly than the molar ratio of $ZnBr_2$ to methyl acrylate (D). The optimum reaction conditions were A2B2C3D1: feeding time = 7 h, reaction time = 5 h, molar ratio of DTBP to methyl acrylate = 0.273, and molar ratio of $ZnBr_2$ to methyl acrylate = 0.035. Under these conditions, the yield of γ-nonalactone reached 70.1 %.

The results of the orthogonal experiments also indicated that the yield of γ-nonalactone decreased with increasing the molar ratio of zinc bromide to methyl acrylate, because the presence of a large amount of $ZnBr_2$ resulted in destruction of free radicals [21]. This result is in agreement with our previous research findings [19, 20].

Table 1 Effects of different experimental Dean–Stark trap conditions

Entry	Dean–Stark trap	Yield (%)[a]
1	None	47.7
2	Filled with water	49.2
3	Filled with *n*-hexanol (top) and water (bottom)	59.3

Reaction conditions: *n*(*n*-hexanol)/*n*(methyl acrylate) = 7, *n*(DTBP)/*n*(methyl acrylate) = 0.273, *n*($ZnBr_2$)/*n*(methyl acrylate) = 0.050, feeding time = 7 h, reaction time = 5 h, reaction temperature = 180 °C

[a] Determined by gas chromatography (GC)

Table 2 Factors and levels selected for orthogonal experiments

	Factor A (feeding time (h)[a])	Factor B (reaction time (h))	Factor C (n(DTBP)/n(methyl acrylate))	Factor D (n($ZnBr_2$)/n(methyl acrylate))
Level 1	6	4	0.164	0.035
Level 2	7	5	0.217	0.047
Level 3	8	6	0.273	0.050

[a] Time at which the mixture of acrylic acid, DTBP, and *n*-hexanol was added to the flask

Table 3 Results of $L_9(3^4)$ orthogonal experiments

No.	A	B	C	D	Yield (%)[a]
1	1	1	1	1	57.3
2	1	2	2	2	63.3
3	1	3	3	3	63.4
4	2	1	2	3	62.0
5	2	2	3	1	70.1
6	2	3	1	2	65.8
7	3	1	3	2	61.4
8	3	2	1	3	60.9
9	3	3	2	1	64.9
K_1^b	61.3	60.2	61.3	64.1	
K_2	66.0	64.8	63.4	63.5	
K_3	62.4	64.7	65.0	62.1	
R^c	4.7	4.6	3.7	2.0	

Reaction conditions: n(*n*-hexanol)/n(methyl acrylate) = 7, reaction temperature = 180 °C

[a] Determined by GC

[b] Average of the sum of experimental results

[c] $R = K_{i,\max} - K_{i,\min}$

Conclusion

In summary, γ-nonalactone was prepared efficiently by free-radical addition of *n*-hexanol to methyl acrylate in the presence of DTBP and zinc bromide using a Dean–Stark trap containing water to absorb the methanol generated.

Experimental

Methyl acrylate (purity, 98 %), *n*-hexanol (purity, 98 %), DTBP (purity, 99 %), and anhydrous zinc bromide (purity, 96 %) were all purchased from Sinopharm Chemical Reagent. GC was performed with a GC9560 system using capillary columns (SE-30 dimethylpolysiloxane, 30 m × 0.32 mm i.d., 0.33 μm film thickness) and under the following conditions: detector and inlet temperature, 250 °C;

temperature program, 130 °C for 1 min, rising to 250 °C at 10 °/min, and then held for 15 min; carrier gas, nitrogen; and average injection volume, 0.5 μl. Compounds were identified by comparing their retention times (R_f) with those of authentic samples. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on an AV 400 NMR spectrophotometer using TMS as internal standard.

General procedure for preparation of γ-nonalactone

Anhydrous zinc bromide (2.10 g, 0.009 mol) and *n*-hexanol (139.02 g, 1.334 mol) were added to a 500-ml round-bottomed flask fitted with a magnetic stirrer, an injector pump, a Dean–Stark trap containing water (15 ml) and *n*-hexanol (10 ml), a condenser, and a thermometer. After the reaction temperature had increased to 180 °C, methyl acrylate (22.29 g, 0.254 mol), DTBP (10.19 g, 0.069 mol), and *n*-hexanol (46.29 g, 0.444 mol) were added via the injector pump over 7 h. During this process, a mixture of *n*-hexanol, methanol, and other low-boiling-point substances collected in the Dean–Stark trap. After 5 h, heating was stopped and the low-boiling-point substances were removed by distillation. γ-Nonalactone was obtained in 70.1 % yield by vacuum distillation. bp, 136–140 °C/13 mmHg; lit. [22] bp, 148–153 °C/13 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53–4.44 (m, 1H), 2.52 (dd, $J = 9.5$, 6.9 Hz, 2H), 2.33–2.25 (m, 1H), 1.87–1.77 (m, 1H), 1.75–1.52 (m, 2H), 1.48–1.25 (m, 6H), 0.92–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.39, 81.11, 35.52, 31.49, 28.86, 27.99, 24.89, 22.47, 13.94.

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